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Licata & Tyrrell
66 East Main Street
Marlton, NJ 08053

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,296	WELSH ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *5-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/05, 3/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-18 are pending in the application.

[2] Applicant's amendment to the claims, filed on 4/16/08, is acknowledged. No changes appear to have been made to the claims by the instant amendment. This listing of the claims replaces all prior versions and listings of the claims.

Election/Restriction

[3] Applicant's election with traverse of Group I, claims 1-4, in the response filed on 4/16/08, is acknowledged. The traversal is on the ground(s) that: 1) the examiner's asserted lack of unity, based on a pharmacophore of the prior art, is unfounded because the pharmacophore of the prior art is not the same as the claimed pharmacophore; and 2) co-examination of the claims of Groups I and II would not require a serious burden on the examiner. Argument 1) is not found persuasive because the claimed pharmacophore is not a contribution over the prior art for reasons set forth below and search burden is not a basis for showing unity of invention according to PCT Rule 13.2. Even if search burden was a basis, it is noted that the invention of Group II recites limitations that are not present in the elected claims of Group I and thus a separate search would be required for the invention of Group II.

The requirement is still deemed proper and is therefore made FINAL.

[4] Claims 5-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made with traverse in the reply filed on 4/16/08.

[5] Claims 1-4 are being examined on the merits.

Information Disclosure Statement

[6] All references cited in the IDSs filed on 10/19/05 and 12/9/05 have been considered by the examiner. A copy of each Form PTO-1449 is attached to the instant Office action.

Priority

[7] Applicants' claim to domestic priority under 35 U.S.C. 119(e) to US provisional application 60/425,037, filed on 11/7/02, is acknowledged.

[8] The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/425,037, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. See particularly the

limitation, "X is any element or group that allows the compound to retain inotropic activity" in claim 3 and the limitation "X is N, O, S, or C" in claim 4.

Specification/Informalities

[9] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Na,K-ATPase Pharmacophore Model---.

[10] The specification's continuing data indicates the instant application is a "continuation-in-part" of provisional application 60/425,037. An application claiming the benefits of a provisional application under 35 U.S.C. 119(e) should not be called a "continuation-in-part" of the provisional application since an application that claims benefit of a provisional application is a nonprovisional application of a provisional application, not a continuation, division, or continuation-in-part of the provisional application. Appropriate correction is required.

[11] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 21, paragraph 50; page 29, paragraph 65) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

Claim Objection

[12] Claim(s) 4 is objected to in the recitation of "X is N, O, S, or C" because X would have improper valency when X is N or C. It is well-known in the art that N has a valency of 3 and C has a valency of 4.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[13] Claim(s) 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1-4 are indefinite in the recitation of "novel" as it is unclear as to how the term is meant to be interpreted in the context of the claim. For example, is the term meant to imply that any pharmacophore model that is "defined by the parameters of Table 4 and Table 5" is novel, is the term meant to indicate that pharmacophore models "defined by the parameters of Table 4 and Table 5" are known in the prior art, yet the claims are limited to only those that are distinguished over the prior art, or is the term meant to be inclusive of only those pharmacophore models that are "novel" and to exclude those pharmacophore models that are obvious to one of ordinary skill in the art? It is suggested that, *e.g.,* applicant delete the term "novel" from the claims.

[b] Claim 3 (claim 4 dependent therefrom) is confusing in the recitation of "...the model produces an Na,K-ATPase inhibitor..." as it is unclear as to whether the claim is

drawn to a "model" or a method of use thereof. See MPEP 2173.05(p).II. In the interest of advancing prosecution, the claim has been interpreted as a "model" and not a method of use thereof.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[14] Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a pharmacophore model. According to the specification, a "'pharmacophore' is a model for developing one or more molecular scaffolds or structure used as the basis for drug development". According to MPEP 2106.IV, "35 U.S.C. 101 defines four categories of inventions that Congress deemed to be the appropriate subject matter of a patent: processes, machines, manufactures and compositions of matter". The claimed pharmacophore is merely a generalized concept and not a compound or article of manufacture. As such the pharmacophore is an abstract idea and is not patent eligible subject matter under 35 U.S.C. § 101. *See In re Warmerdam*, 33 F.3d 1354, 1360, 31 USPQ2d 1754, 1759 (Fed. Cir. 1994).

[15] Even if the model of claims 3-4 is shown to be patent eligible subject matter as a manufacture or composition of matter, the following rejection still applies. Claims 3-4 are rejected under 35 U.S.C. 101 because the claims are directed to neither a "process"

nor a "machine," but rather embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes of invention in the alternative only. See MPEP 2173.05(p).II.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[16] Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to a genus of pharmacophore models as defined by the parameters of Table 4 and Table 5. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in

possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification describes only a single representative species of pharmacophore models as encompassed by the claimed genus, *i.e.*, the pharmacophore model made by the method at p. 28, paragraph 64 to p. 31, paragraph 69. The specification fails to describe any additional representative species of the recited genus of structural coordinates. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the recited genus of pharmacophore models encompasses species that are widely variant with respect to their structures, particularly as the "parameters of Table 4 and Table 5" are not required in the claims to be relative to any particular 3-D structural model or residues thereof. As such, the disclosure of the single representative species of pharmacophore models as noted above is insufficient to be representative of the attributes and features of *all* species encompassed by the recited genus of structural coordinates.

Given the lack of description of a representative number of candidate modulators or potential inhibitors, the specification fails to sufficiently describe the claimed invention

in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[17] Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are so broad as to encompass any pharmacophore model "as defined by the parameters of Table 4 and Table 5", wherein the model can represent the binding pocket of essentially any polypeptide that has "the parameters of Table 4 and Table 5". The scope of the claims is not commensurate in scope with the enablement provided by the specification. In this case, the specification

is limited to being enabling for a pharmacophore model as made according to the method set forth in the specification at p. 28, paragraph 64 to p. 31, paragraph 69.

The lack of guidance and working examples: In this case, the specification discloses certain feature of a pharamcophore at Tables 4 and 5 (pp. 26-27 of the specification). However, the specification fails to disclose the structural coordinates of the model of Na,K-ATPase that was used to determine these characteristics. Without such a 3-D model, a skilled artisan would be unable to reconstruct the three dimensional positions of each point of the pharmacophore such that it would be useful in the identification and screening of potential Na,K-ATPase ligands. While it is acknowledged that the specification discloses a method for making a model of Na,K-ATPase and a pharmacophore model therefrom, (specification at p. 28, paragraph 64 to p. 31, paragraph 69), however, this method requires several user-defined steps that are subjective in nature.

The high level of unpredictability in the art: It is highly unpredictable as to whether a pharmacophore model defined solely by Table 4 and Table 5 parameters will have the same characteristics as that produced according to the method set forth in the specification at p. 28, paragraph 64 to p. 31, paragraph 69, particularly as the parameters of Table 4 and Table 5 are not associated with any 3-D structural model or residues thereof. As noted above, the specification lacks any teaching of any model that one of ordinary skill in the art can employ for making the claimed pharmacophore. The specification discloses some drawing figures that show a two dimensional representation of a modeled structure and provides data disclosing some characteristics

of a pharamacophore as encompassed by the claims. However, a 3-D model cannot be reproduced based on two dimensional figures alone – it requires a three-dimensional model defined by specific structural coordinates. While modeling methods are known in the art can construct a model as described in the specification, it is more likely than not the resulting model will be different from that used to generate the pharmacophore produced by applicant. It is well-known in the prior art (see, *e.g.*, Cohen et al., *J. Med. Chem.* 33:883-894, 1990) that homology modeling requires four essential steps: (i) Sequence alignment of a protein with known three-dimensional structure determined by experimental method to that of a protein with unknown three-dimensional structure using one of several known algorithms; (ii) Construct a template of the three-dimensional structure of the protein with known three-dimensional structure. Place the atoms of identical residues and those of conserved residues in the same positions as those of the template; (iii) The remaining residues, which include insertion, deletion, and non-conservative substitution, are usually modeled by one of two methods: (a) searching in the protein structure databases for structure element comprising a fragment which its sequence is identical or homologues to the sequence of interest using several software packages; (b) *de novo* modeling the fragments of interest, (c) using combination of (a) or (b); (iv) Manually minimizing the number of high-energy atomic contact, and minimize the energy of the resulting structure.

It should be noted that in each the above four steps there several subjective choices that have to be made by the modeler. Choices made by the modeler of the algorithm and the operational parameters in carrying out a particular step. The human

choice mades in the selection of a particular structure element in steps (iii) and the manual movement of atoms in step (iv). Thus, describing general modeling method would not provide the same structure that the applicants have used to carry out their invention. Without the modeled structure obtained by the applicants, one of ordinary skill in the art would come to the conclusion that applicant's pharmacophore cannot be accurately reproduced.

The amount of experimentation required: It is not routine in the art to generate all pharmacophore models as broadly encompassed by the claims without reference or relation to a particular 3-D structure or residues thereof.

Thus, in view of the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the significant amount of experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the claimed invention. As such, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[18] Claim(s) 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holtje et al. (*Phamazie* 47:691-697, 1992; "Holtje") and the legal precedent of In re Gulack 217 USPQ 401 (Fed. Cir. 1983). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103. The claims are drawn to a pharmacophore model as defined by the parameters of Table 4 and Table 5.

According to the abstract of Holtje, "Using molecular modelling methods, several digitalis-unlike compounds such as chlormadinol acetate and cassaine, which bind to the digitalis receptor and inhibit the Na+/K(+)-ATPase were compared with cardenolides as a standard. The interaction energies of this group of compounds with various probes such as a methyl group or a NH-amid group were calculated using GRID and compared using GRAD. A pharmacophore model was derived, which describes all corresponding inotropic substrates. On this basis and including experimental knowledge on the Na+/K(+)-ATPase a receptor model was developed" (emphasis added). A 2 dimensional representation of the pharmacophore of Holtje is shown at p. 696, Figures 11 and 12. It

is noted that the pharmacophore of Holtje was constructed based on publicly available structural coordinates (see p. 696, column 1).

In *Gulack*, the Court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the differences between the pharmacophore of Holtje and the claimed pharmacophore is limited to the "parameters of Table 4 and Table 5". If the difference between the prior art and the claimed invention as a whole is limited to descriptive material, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the "parameters of Table 4 and Table 5" have no functional relationship with any other entity and thus are considered to be non-functional descriptive material. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Holtje using a pharmacophore with the "parameters of Table 4 and Table 5", which, according to *In re Gulack,* do not distinguish the claimed pharmacophore from that taught by the cited prior art reference. One of ordinary skill in the art would have been motivated to make a pharmacophore with "parameters of Table 4 and Table 5"because of the teachings of Holtje and would have had a reasonable expectation of success for making the claimed pharmacophore because of the teachings of Holtje. Therefore, claims 1-4 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: According to applicant in the response filed on 4/16/08, "Holtje et al. disclose modeling the compounds themselves, without consideration of the features of the ligand binding pocket…As is clear from a comparison of the Holtje et al. compounds with compounds derived from the pharmacophore model of the present invention, *e.g.,* as in claim 3, the basic scaffold of the Holtje et al. compounds is distinct from those of the present invention".

Applicant's argument is not found persuasive because the only different between the pharmacophore of Holtje and the pharmacophore of claims 1-4 is non-functional descriptive material, which, as noted above, cannot distinguish the claimed pharmacophore from that taught by the cited prior art reference.

Citation of Relevant Art

[19] The art made of record and not relied upon is considered pertinent to applicant's disclosure. 1) Keenan et al. *FASEB J.* Vol. 17, Abstract 582.7; 2) Ball, Jr. et al. *Ann. NY Acad. Sci.* 986:296-297, 2003; and 3) Keenan et al. *J. Mol. Graphics Model.* 23:465-475, 2005.

Conclusion

[20] Status of the claims:

Claims 1-18 are pending.

Claims 5-18 are withdrawn from consideration.

Claims 1-4 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656